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# **Confirmatory Study of Time-Dependent Computed Tomographic Perfusion Thresholds for use in Acute Ischemic Stroke**

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Tables: 1; Figures: 1.

Cover title: Time-Variant CTP Thresholds for Ischemic Infarct

## Abstract

**Background and Purpose**—Computed tomographic perfusion (CTP) thresholds associated with follow-up brain infarction may differ by time from symptom onset to imaging and reperfusion. We confirm CTP thresholds over time to imaging and reperfusion in acute ischemic stroke (AIS) patients from the HERMES data.

**Methods**—Patients with occlusion on CT angiography were acutely imaged with CTP. Non-contrast CT and MR-DWI at 24-48 hours defined follow-up infarction. Reperfusion was assessed on conventional angiogram.  $T_{\max}$ , cerebral blood flow (CBF), and cerebral blood volume (CBV) maps were derived from delay insensitive CTP post-processing. These parameters were analyzed using receiver operator characteristics to derive optimal thresholds based on time from stroke onset-to-CTP or to reperfusion. ANOVA and linear regression were used to test whether the derived CTP thresholds were different by time.

**Results**—137 patients were included.  $T_{\max}$  thresholds of  $>15.7$  s and  $>15.8$  s and absolute CBF thresholds of  $<8.9$  and  $<7.5$   $\text{mL}\cdot\text{min}^{-1}\cdot 100\text{ g}^{-1}$  for gray matter (GM) and white matter (WM) respectively were associated with infarct if reperfusion was achieved  $<90$  min from CTP with stroke onset-to-CTP  $<180$  min. The discriminative ability of CBV was modest. There were no statistically significant relationships between stroke onset-to-CTP time and  $T_{\max}$ , CBF, and CBV thresholds (all  $p>0.05$ ). A statistically significant relationship was observed between CTP-to-reperfusion time and the optimal thresholds for  $T_{\max}$  ( $p<0.001$ ) and CBF ( $p<0.001$ ). Similar but more modest relationship was noted for onset-to-reperfusion time and optimal thresholds for CBF ( $p\leq 0.01$ ).

**Conclusions**—CTP thresholds based on stroke onset and imaging time and taking into account time needed for reperfusion may improve infarct prediction in patients with acute ischemic stroke.

**Key Words:** Acute ischemic stroke, computed tomographic perfusion.

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Recent trials have shown benefit of fast and effective endovascular treatment (EVT) in acute ischemic stroke (AIS) patients with intracranial occlusions.<sup>1</sup> To help with triage and transport decisions as well as clinical decision making, physicians need to know how much brain tissue is likely to infarct by the time the patient reaches a tertiary center and endovascular therapy is administered. In a proof of principle analysis from an imaging cohort study, we showed that CTP thresholds estimating follow-up infarct depends on time from imaging to reperfusion.<sup>2</sup> Here, we use data from recent positive endovascular trials obtained through the HERMES collaboration<sup>1</sup> to provide confirmatory evidence on time-dependent CTP thresholds that identify brain tissue that will likely infarct at different times from quality reperfusion.

## **Methods**

### **Patients**

Data are from the HERMES Collaboration.<sup>1</sup> The data that support the findings of this study are available from the corresponding author upon reasonable request. Subjects who had (1) baseline CTP imaging with  $\geq 8$  cm z-axis coverage; (2) underwent EVT; (3) had reperfusion assessed on conventional angiography at end of EVT using the modified thrombolysis in cerebral infarction [mTICI]); and (4) had 24-hour follow-up imaging on MR DWI or non-contrast CT (NCCT) were included. All trials had ethics approval from institutional review boards. Written informed consent was obtained from each patient. Each baseline CTP was processed by commercially available delay-insensitive deconvolution software (CT Perfusion 4D; GE Healthcare). Details on image processing are described in the Supplemental Methods.

### **Statistical Analysis**

Differences between groups were tested using one-way analysis of variance (ANOVA) for parametric data, Kruskal–Wallis test for nonparametric data, and the Fisher’s test for categorical outcomes. Patients were stratified into 2 groups: (1) stroke onset-to-CTP <180 min and (2) ≥180 min. These groups were then subdivided into 3 subgroups according to CTP-to-reperfusion time: (1) <90 min reperfusion, (2) 90 to 180 min reperfusion, and (3) no acute reperfusion. CTP parameters (CBF, CBV,  $T_{\max}$ ) from each subgroup were pooled for ROI-1 (infarct on follow-up imaging) and ROI-2 (ipsilateral brain excluding infarct). Pooled data were then input into a logistic regression model to generate a receiver operating characteristic (ROC) for each parameter. ROC were analyzed to determine optimal CTP thresholds associated with follow-up infarction. The areas under the curves (AUC) of all CTP parameters were compared. Patient level data were analyzed in the same manner as pooled data to derive optimal CTP parameters at an individual level. Linear regression was used to determine the association between optimal CTP thresholds derived at the individual level and various interval times (continuous time analysis). Two-sided alpha <0.05 was considered statistically significant.

## Results

137 patients receiving EVT were included (Supplemental Table I). Details of patients excluded are in Supplemental Results.

In pooled analysis, for patients with onset-to-CTP <180 min (n=90),  $T_{\max}$  and CBF were better than CBV in predicting follow-up infarct in all three subgroups i.e. CTP-to-mTICI-2b/3 reperfusion <90 min, 90 to 180 min, and no acute reperfusion. Similar findings were found for patients with onset-to-CTP ≥180 min (n=47). Optimal  $T_{\max}$ , CBF, and CBV thresholds

associated with follow-up infarct from patient-level data analysis were similar. (Table 1 and Supplemental Table II)

There was no statistically significant relationship between stroke onset-to-CTP time and the  $T_{max}$ , CBF, and CBV thresholds ( $p>0.05$ ). A statistically significant relationship was observed between CTP-to-reperfusion-time and optimal thresholds for  $T_{max}$  ( $p<0.001$  for continuous time analysis;  $r=-0.532$  and  $-0.37$  for GM and WM, respectively) and CBF ( $p<0.001$  for continuous time analysis;  $r=0.445$  and  $0.579$  for GM and WM, respectively). (Supplemental Figure II).

When patients were stratified by onset-to-CTP time, a statistically significant relationship was observed between CTP-to-reperfusion-time and optimal CTP thresholds for patients with stroke onset-to-CTP  $<180$  mins for  $T_{max}$  ( $p<0.001$ ;  $r=-0.644$  and  $-0.433$  for GM and WM, respectively) and CBF [ $p<0.001$ ;  $r=0.545$  and  $0.736$  for GM and WM, respectively]. Similar significant relationship between CTP-to-reperfusion-time and optimal thresholds for patients with stroke-onset-to-CTP  $\geq 180$  mins was noted for CBF [ $p=0.003$ ;  $r=0.516$  and  $p=0.04$ ;  $r=0.406$  for GM and WM, respectively], but not for the  $T_{max}$  or CBV. (Figure 1)

A statistically significant relationship was observed between stroke onset-to-reperfusion time and optimal thresholds for  $T_{max}$  for GM ( $p<0.01$ ;  $r=-0.277$ ) and CBF [ $P=0.014$ ;  $r=0.243$  and  $p<0.01$ ;  $r=0.294$  for GM and WM, respectively].  $T_{max}$  for WM and CBV did not show any significant differences in optimal thresholds ( $P>0.1$ ). When patients were stratified by onset-to-CTP-time, a statistically significant relationship between onset-to-reperfusion-time and optimal thresholds was observed for patients presenting with onset-to-CTP  $<180$  mins for  $T_{max}$  ( $p<0.001$ ;  $r=-0.477$  and  $p<0.01$ ;  $r=-0.372$  for GM and WM, respectively) and CBF ( $p<0.01$ ;  $r=0.381$  and  $p<0.01$ ;  $0.546$  for GM and WM, respectively). No statistically significant relationship was observed for

$T_{\max}$ , CBF, CBV parameter for both GM and WM for the patients presenting with stroke-onset-to-CTP $\geq$ 180 mins. (Supplemental Figure III).

## Discussion

Current perfusion paradigms use only one threshold (e.g. rCBF <30%) to estimate infarction in all patients.<sup>3</sup> These results from the recent positive endovascular stroke trials however, provide confirmatory evidence that optimal perfusion thresholds (e.g. CBF) associated with infarction should progressively increase over time as infarcts grow into penumbra.<sup>2,4</sup> Unlike previous work that showed a relationship between optimal perfusion thresholds and imaging-to-reperfusion time, this analysis, more intuitively, shows that these thresholds are also dependent on onset-to-reperfusion-time.<sup>2</sup>

Interestingly, the association between optimal CTP thresholds and onset-to-reperfusion time was weaker when patients presented late. One reason could be that infarct growth over time may be slower amongst many late presenters, resulting in a weaker association between CTP thresholds estimating ischemic core and time-to-reperfusion. Another reason could be that patients with wake-up strokes present late; in such patients, stroke onset time is often imprecise. These results also show that unlike CBF and  $T_{\max}$ , CBV is a sub-optimal CTP parameter for estimating ischemic core. Reasons include CBV being affected by time-density curve truncation and the fact that the relationship between severity of ischemia and CBV is non-linear.<sup>2</sup>

This study has limitations. Differences between the deconvolution algorithm used in this analysis vs. other algorithms may affect  $T_{\max}$ . CBF thresholds that are used to estimate infarction should however be similar across algorithms. Second, only a proportion of follow up scans were DWI



images. Images with more precise follow up infarct delineation may improve the validity of these results.

In conclusion, these results demonstrate that optimal CTP thresholds associated with follow-up infarction are dependent on time from stroke symptom onset to when quality reperfusion is likely to be achieved. In future, automated software that use perfusion to help physicians make treatment decisions should use variables such as time as model inputs when estimating infarction.

### **Disclosures**

Dr Qiu reports grants from Canadian Institute Health Research during the conduct of the study. Dr Menon reports a patent to Systems of triage in acute stroke issued. Dr Goyal reports personal fees from Medtronic, personal fees from Stryker, and personal fees from microvention outside the submitted work; in addition, Dr Goyal has a patent to Systems of acute stroke diagnosis issued and licensed. Dr. Lee has a licensing agreement with GE Healthcare for the CT Perfusion software. Dr Hill reports grants from Covidien (Medtronic), grants from Medtronic, grants from Stryker, grants from Boehringer-Ingelheim, and grants from Alberta Innovates outside the submitted work; in addition, Dr Hill has a patent to Systems and Methods for Assisting in Decision-Making and Triaging for Acute Stroke Patients issued. Dr Brown reports personal fees from University of Calgary during the conduct of the study; personal fees from Medtronic outside the submitted work. Dr Boers reports Nico.lab. Dr. Davalos reports grants from MEDTRONIC. Dr Demchuk reports personal fees from Medtronic during the conduct of the study. Dr Dippel reports grants from Dutch Heart Foundation, grants from AngioCare BV, grants from Covidien/EV3®, grants from MEDAC GmbH/LAMEPRO, grants from Penumbra Inc., grants from Top Medical/Concentric, and grants from Stryker during the conduct of the study; grants from Dutch Heart Foundation, grants from Brain Foundation Netherlands, grants from The Netherlands Organisation for Health Research and Development, grants from Health Holland Top Sector Life Sciences & Health, grants from Stryker European Operations BV, grants from Penumbra Inc., grants from Medtronic, and grants from Thrombolytic Science, LLC outside the submitted work. Dr Saver reports personal fees from Medtronic during the conduct of the study. Dr Jovin reports other from Anaconda, other from Route92, other from Viz.ai, personal fees from Cerenovus, other from FreeOx, and grants and non-financial support from Stryker Neurovascular outside the submitted work. Dr Majoie reports grants from CVON/Dutch Heart Foundation, grants from TWIN Foundation, grants from European Commission, grants from Dutch Health Evaluation program, and grants from Stryker outside the submitted work; and shareholder Nico-lab, a company that focuses on the use of artificial intelligence for medical image analysis (modest). Dr. White reports grants from Microvention Terumo, grants from Stryker, grants from Penumbra, grants from Medtronic, personal fees from Microvention, outside the submitted work. Dr Muir reports personal fees and non-financial support from Boehringer Ingelheim, personal fees from Bayer, and personal fees from Daiichi Sankyo outside the submitted work. Dr Mitchell reports other from Medtronic, other from Stryker, and other from Codman Johnson & Johnson during the conduct of the study. Other authors have nothing to disclose.

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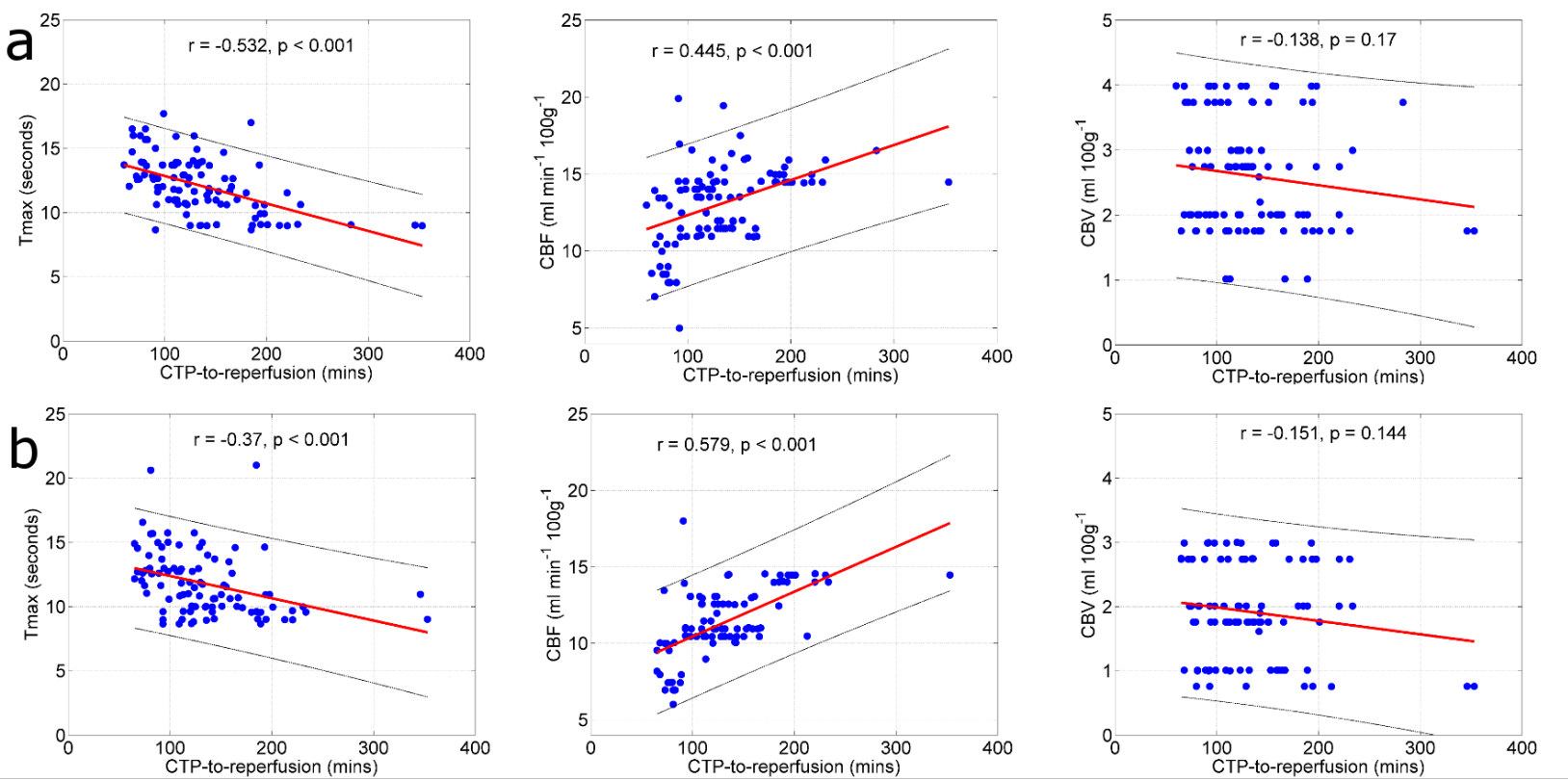
## TABLES

Table 1. Optimal CTP thresholds for infarction when reperfused <90 min, 90-to-180 min, and no acute reperfusion.

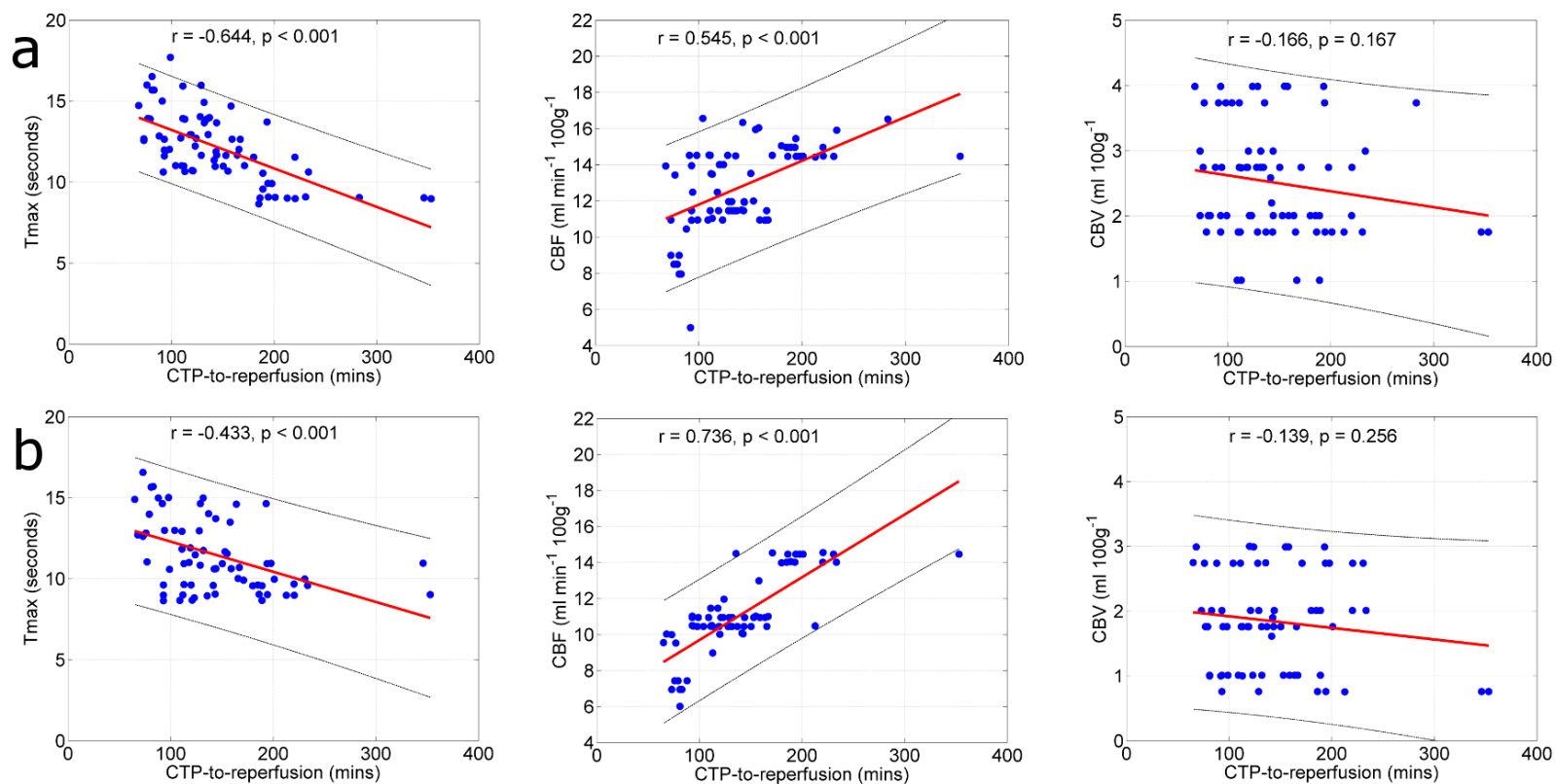
Onset-to-CTP Time(min)	CTP-to-Reperfusion time(min)		<b>T<sub>max</sub> (s)</b>		<b>CBF(mLmin<sup>-1</sup> ·100g<sup>-1</sup>)</b>		<b>CBV(mL100g<sup>-1</sup>).</b>	
			<b>GM</b>	<b>WM</b>	<b>GM</b>	<b>WM</b>	<b>GM</b>	<b>WM</b>
<180	<90(n=11)		<b>15.7</b>	<b>15.8</b>	<b>8.9</b>	<b>7.5</b>	<b>3.0</b>	<b>2.0</b>
		AUC[95%CI]	0.93[0.91,0.95]	0.89[0.86,0.92]	0.92[0.89,0.95]	0.88[0.85,0.91]	0.61[0.59,0.63]	0.65[0.62,0.69]
		Sens,Spec	0.81,0.87	0.77,0.8	0.82,0.82	0.78,0.88	0.54,0.62	0.59,0.61
	90-180(n=44)		<b>12.0</b>	<b>11.0</b>	<b>11.5</b>	<b>10.4</b>	<b>3.0</b>	<b>1.7</b>
		AUC[95%CI]	0.92[0.90,0.94]	0.88[0.86,0.90]	0.89[0.85,0.93]	0.91[0.89,0.93]*	0.74[0.71,0.77]	0.71[0.68,0.74]
		Sens,Spec	0.89,0.83	0.82,0.78	0.76,0.84	0.79,0.88	0.8,0.56	0.49,0.87
	No Acute Reperfusion(n=35)		<b>10.1</b>	<b>10.1</b>	<b>15.0</b>	<b>14.0</b>	<b>3.0</b>	<b>1.0</b>
		AUC[95%CI]	0.90[0.88,0.92]	0.87[0.85,0.89]	0.92[0.90,0.94]	0.90[0.89,0.92]*	0.64[0.61,0.67]	0.62[0.60,0.64]
		Sens,Spec	0.84,0.76	0.78,0.75	0.81,0.83	0.77,0.9	0.57,0.64	0.57,0.63
>180	<90(n=9)		<b>13.7</b>	<b>13.8</b>	<b>9.2</b>	<b>8.0</b>	<b>2.0</b>	<b>2.0</b>
		AUC[95%CI]	0.83[0.80,0.86]	0.82[0.77,0.87]	0.90[0.87,0.93]*	0.90[0.86,0.94]*	0.74[0.69,0.79]	0.67[0.63,0.71]
		Sens,Spec	0.77, 0.77	0.75,0.78	0.77,0.82	0.79,0.93	0.84,0.59	0.63,0.61
	90-180(n=19)		<b>11.7</b>	<b>11.8</b>	<b>14.2</b>	<b>12.5</b>	<b>3.0</b>	<b>2.0</b>
		AUC[95%CI]	0.87[0.85,0.89]	0.86[0.84,0.88]	0.90[0.87,0.93]	0.87[0.85,0.89]	0.58[0.53,0.63]	0.55[0.51,0.59]
		Sens,Spec	0.77,0.76	0.76,0.76	0.83,0.79	0.72,0.81	0.49,0.64	0.52,0.58
	No Acute Reperfusion(n=19)		<b>10.0</b>	<b>10.0</b>	<b>15.4</b>	<b>14.4</b>	<b>3.8</b>	<b>2.7</b>
		AUC[95%CI]	0.88[0.86,0.90]	0.88[0.86,0.90]	0.89[0.87,0.91]	0.85[0.82,0.88]	0.57[0.54,0.60]	0.62[0.59,0.65]
		Sens,Spec	0.82,0.75	0.8,0.76	0.78,0.81	0.82,0.7	0.45,0.65	0.63,0.54

**Figure 1.** Continuous-time analysis using patient level data for optimal computed tomographic perfusion (CTP) threshold associated with follow-up infarction versus CTP-to-reperfusion time in gray matter (A) and white matter (B).

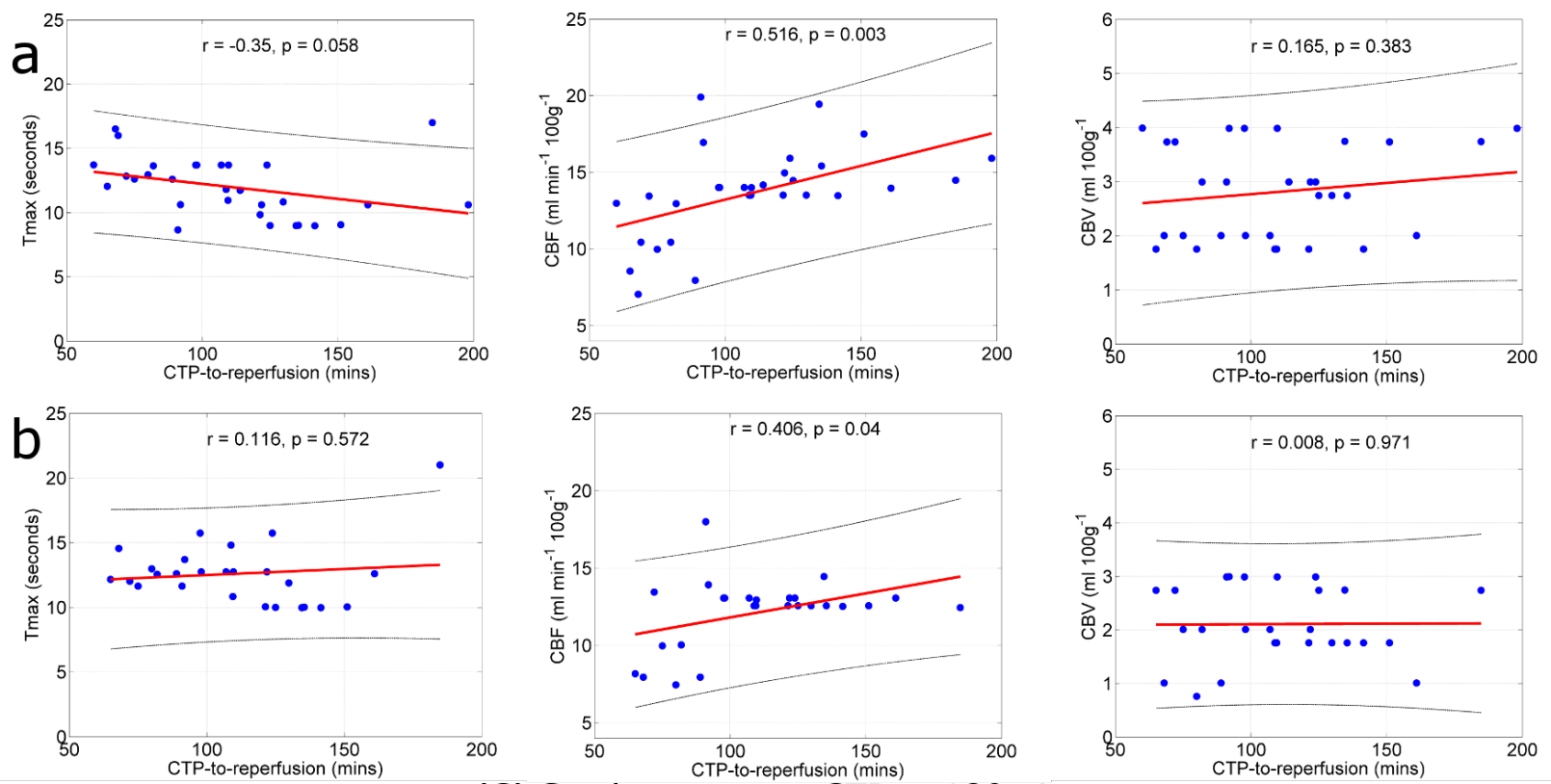
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(A) All patients



(B) Stroke-onset-to-CTP < 180mins



(C) Stroke-onset-to-CTP  $\geq 180$  mins